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STUDIES ON THE ALKALOIDS OF CEPHALOTAXUS
IX. SEMI-SYNTHESIS OF CEPHALOTAXINE ANALOGUES AND THEIR ANTILEUKAEMIA ACTIVITY

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Abstract. The semi-synthesis of 17 new esters of cephalotaxine and their antitumour actions are reported. The results of pharmacological experiments show that 1, 2, 2 + 3, 6 and 8 had significant antitumour activity, while 4, 5, 15 and 16 had moderate antitumour activity. By comparing their chemical structures and antitumour activities, the structure-effect relationship of these alkaloids has been provisionally explored.

Keywords. Cephalotaxus; Harringtonine analogues; Antitumour activity

Since the actions of homoharringtonine etc. in the treatment of leukaemia were discovered [1-3], many research teams have developed studies into the structure-effect relationship of harringtonine analogues [4-5]. Viewed from their chemical structure, natural ester bases are connected to different acyl side chains, and they have similar antileukaemia activity, showing that the acyl side chain is variable. However, these side chains all contain a methyl ethanoate group, and the difference is only in different R_1 groups (Figure 1). The four ester bases which were separated early had R_1 groups which were straight chain alkanes, but we have recently isolated two new anticancer harringtonine alkaloids [6], their R_1 groups being a benzyl group and tetrahydrofuran group with physiological activity respectively. With these as the first compounds derived, 10 analogues have been synthesized 1 (epimer) - 10. The already-known maytansine is a compound with anticancer activity, and its active branch chain [7, 8] has similarities to the acyl group branch chain of harringtonine. We have therefore synthesized this branch chain and connected it to the cephalotaxine parent body to yield a total of 4

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compounds 11 - 14. We have also synthesized three simple ester base analogues 15, 16 and 17.

[Equation] Key: 1: R_1=CH_2Ph (epimer)

Cephalotaxine was allowed to react with α-ketoyl chloride (obtained from the reaction of the corresponding α-ketonic acid with oxalyl chloride), to yield α-ketoyl harringtonine through acylation. This then underwent a Reformatsky equation with methyl bromoethanoate so that compounds 1, 2 + 3, 4 + 5, 6 + 7 and 15 could be obtained. The three pairs of epimers 2 + 3, 4 + 5 and 6 + 7 could be separated by HPLC in a semi-prepared column and identified by ^{1}HNMR. 2, 4 and 6 were 2'*R* form; 3, 5 and 7 were 2'*S* form.

Compounds 8 and 9 were obtained from harringtonine and homoharringtonine respectively through refluxing dehydration catalysed by *p*-toluene sulphonic acid. Compound 10 was obtained from harringtonine through dehydration using methyl sulphonyl chloride.

Esterification of the corresponding branch chain acid with cephalotaxine yielded compounds 11 - 14, 16 and 17.

The abovementioned compounds were screened in vitro with white mice leukaemia P 388, the results of which are listed in the following table.

Table 1. Growth inhibition (%) of cephalotaxine esters against leukaemia P 388 cell *in vitro*

Compd	100 μg/ml	10 μg/ml	1 μg/ml	Compd	100 μg/ml	10 μg/ml	1 μg/ml
1	98.6	100	100	9	99.3	64.8	0
2	99.3	100	95.1	10	100	95.1	0
2 + 3	98.6	99.3	97.2	11	0	0	0
4	97.9	97.2	18.3	12	0	0	0
5	99.7	96.8	81.0	13	0	0	0
4 + 5	100	95.7	68.1	14	0	0	0
6	98.7	99.7	90.5	15	96.0	78.7	19.3
7	0	0	0	16	95.3	76.7	8.6
6 + 7	100	86.2	15.7	17	90.7	42.0	0
8	100	100	97.9	Homoharringtonine	100	99.3	99.3

Experimental Components

The melting point was measured with a Kofler micro-melting point instrument, which had not been calibrated. Rotation was measured with a Jasco Dip-181 polarimeter. A Perkin-Elmer 599 B instrument was used for IR measurement, LRMS was measured with a MAT-44 instrument, HRMS with a MAT-711 instrument, and ^{1}HNMR with a Bruker Am-400. The silica gel was produced by the Qingdao Marine Chemical Engineering Works, and the developer was iodine vapour or a Dragendorff reagent.

Compound 1

The preparation method and spectroscopic data have already been reported in another paper[6].

Compounds 2 and 3

500 mg of γ-phenyl-α-oxobutanoic acid was allowed to react with an equivalent amount of 10% Na_2CO_3 to yield the sodium salt. 100 mg of the dried sodium salt was used for the preparation method exactly as for 1, to yield 40 mg of a mixture of 2 + 3, with a two step yield of 25%. $[\alpha]_D$-68° (c 0.37, $CHCl_3$). IR (KBr) cm^{-1} 3420, 1740, 1655, 1505, 1490, 1370, 1220, 1035, 930. EIMS m/z 549 (M^+), 518, 447, 417, 315, 314, 299, 298 (100), 297, 282, 266, 254.

20 mg of the mixture was taken and separated using HPLC in accordance with the litera ture [11] to yield 5 mg of 2 and 4 mg of 3.

2 (2'*R*) was a colourless oily substance, ^{1}HNMR (CD_3COCD_3) δ ppm 7.24 (5H, m, Ph-H), 6.62 (1H, s, C_{17}-H), 6.60 (1H, s, C_{14}-H), 6.03 (1H, d, J = 9.5 Hz, C_3-H), 5.88, 5.78 (2H, -OCH_2O-), 5.30 (1H, s, C_1-H), 3.94 (1H, d, J = 9.8 Hz, C_4-H), 3.72 (3H, s, -OCH_3), 3.50 (3H, s, -$COOCH_3$), 2.23, 1.98 (2H, dd, J = 16 Hz, C_3-H).

3 (2'*S*) was a colourless oily substance, ^{1}HNMR (CD_3COCD_3) δ ppm 7.16 (5H, m, Ph-H), 6.62 (1H, s, C_{17}-H), 6.47 (1H, s, C_{14}-H), 5.88 (1H, d, J = 10 Hz, C_3-H), 5.79 (2H, -OCH_2O-), 5.24 (1H, s, C_1-H), 3.91 (1H, d, J = 9.7 Hz, C_4-H), 3.70 (3H, s, -OCH_3), 3.63 (3H, s, -$COOCH_3$), 2.71, 2.59 (2H, dd, J = 16.4 Hz, C_3-H).

Compounds 4 and 5

200 mg of dry sodium 3-ene-4-phenyl-α-oxobutanoate was used for the preparation method exactly as in 1, to yield 70 mg of a mixture of 4 + 5, with a two step yield of 18%. IR (KBr) cm^{-1} 3450, 1740, 1655, 1505, 1490, 1435, 1370, 1220, 1035, 930, 750, 695. EIMS m/z 547 (M^+), 532, 517, 371, 370, 315, 314, 300, 299, 298, 282, 266, 254.

20 mg of the mixture was separated by HPLC to yield 4.6 mg of 4 and 3.3 mg of 5.

4 (2'*R*) was a colourless oily substance, $[\alpha]_D$-116.4° (c 0.196, $CHCl_3$). ^{1}HNMR (CD_3COCD_3) δ ppm 7.37 (4H, m, Ph-H), 7.29 (1H, m, Ph-H), 6.71 (1H,d, J = 15.8 Hz, CH=), 6.62 (1H, s, C_{17}-H), 6.61 (1H, s, C_{14}-H), 6.10 (1H, d, J = 15.7 Hz, CH=), 5.95 (1H, d, J = 9.3 Hz, C_3-H), 5.86 (2H, d, -OCH_2O-), 5.26 (1H, s, C_1-H), 3.86 (1H, d, J = 9.7 Hz, C_4-H), 3.65 (3H, s, -OCH_3), 3.53 (3H, s, -$COOCH_3$).

5 (2'*S*) was a colourless oily substance, $[\alpha]_D$-80.5° (c 0.17, $CHCl_3$). ^{1}HNMR (CD_3COCD_3) δ ppm 7.32 (5H, m, Ph-H), 6.62 (1H, d, J = 15.7 Hz, Ch=), 6.58 (1H, s, C_{17}-H), 6.45 (1H, s, C_{14}-H), 5.84 (1H, d, J = 9.3 Hz, C_3-H), 5.79 (2H, d, J= 1.4 Hz, -OCH_2O-), 5.48 (1H, d, J = 15.6 Hz, CH=), 5.25 (1H, s, C_1-H), 3.89 (1H, d, J = 9.7 Hz, C_4-H), 3.71 (3H, s, -OCH_3), 3.63 (3H, s, -$COOCH_3$), 2.89, 2.51 (2H, dd, J = 16.2 Hz, C_3-H).

Compounds 6 and 7

220 mg of dry sodium phenyl-α-oxopentanoate was used according to the preparation method for 1, to yield 230 mg of a mixture of 6 + 7, with a two step yield of 62%, IR (KBr) cm^{-1} 3500, 1745, 1655, 1505, 1490, 1370, 1230, 1080, 1030, 925, 750, 700. EIMS m/z 563 (M^+), 532, 315, 314, 299, 298 (100), 297, 282, 267, 265, 228, 150.

20 mg of the mixture was separated by HPLC to yield 5 mg of 6 and 4 mg of 7.

6 (2'*R*) was a colourless oily substance, $[\alpha]_D$-103° (c 0.79, $CHCl_3$). ^{1}HNMR (CD_3COCD_3) δ ppm 7.29, 7.17 (5H, m, Ph-H), 6.60 (1H, s, C_{17}-H), 6.56 (1H, s, C_{14}-H), 5.94 (1H, d, J = 9.9 Hz, C_3-H), 5.88 (2H, -OCH_2O-), 5.23 (1H, s, C_1-H), 3.86 (1H, d, J = 9.9 Hz, C_4-H), 3.68 (3H, s, -OCH_3), 3.49 (3H, s, -$COOCH_3$), 2.16, 1.86 (2H, dd, J = 16.3 Hz, C_3-H).

7 (2'*S*) was a colourless oily substance, $[\alpha]_D$-119° (c 0.62, $CHCl_3$). ^{1}HNMR (CD_3COCD_3) δ ppm 7.25, 7.16 (5H, m, Ph-H), 6.69 (1H, s, C_{17}-H), 6.66 (1H, s, C_{14}-H), 5.85 (1H, d, J = 9.9 Hz, C_3-H), 5.84 (2H, d, -OCH_2O-), 5.21 (1H, s, C_1-H), 3.89 (1H, d, J = 9.6 Hz, C_4-H), 3.67 (3H, s, -OCH_3), 3.60 (3H, s, -$COOCH_3$), 2.65, 2.48 (2H, dd, J = 16.5 Hz, C_3-H).

Compound 8

The preparation method and spectroscopic data have already been reported in another paper[6].

Compound 9

50 mg of homoharringtonine was used according to the preparation method for 8, to yield 40 mg of 9 with a yield of 83%. Oily substance $[\alpha]_D$-71.8° (c 0.48, $CHCl_3$). IR (KBr) cm^{-1} 1735, 1655, 1505, 1490, 1450, 1370, 1225, 1040, 925, 800. EIMS m/z 527 (M^+), 496, 315, 314, 300, 299, 298 (100), 282, 267, 266, 254, 227, 150. ^{1}HNMR (CD_3COCD_3) δ ppm 6.61 (1H, s, C_{17}-H), 6.57 (1H, s, C_{14}-H), 5.88 (2H, d, -OCH_2O-), 5.82 (1H, d, J = 10 Hz, C_3-H), 5.24 (1H, s, C_1-H), 3.89 (1H, d, J = 9.7 Hz, C_4-H), 3.70 (3H, s, -OCH_3), 3.49 (3H, s, -$COOCH_3$), 2.30 (2H, dd, J = 15.3 Hz, C_3-H), 1.15 (3H, s, -CH_3), 1.70 (3H, s, -CH_3).

Compound 10

53 mg of harringtonine was dissolved in 1 ml of dry dichloromethane, and 0.024 ml of anhydrous triethylamine was added dropwise with agitation. It was cooled to -25°C, and 0.0078 ml of double-distilled methyl sulphonyl chloride was added dropwise, after which the

temperature was raised to -5°C. Agitation was carried out for 0.5 h, and the reaction liquid was diluted with 5 ml of dichloromethane. The organic layer was washed twice each in sequence with 10% Na_2CO_3 and saturated saline and dried with anhydrous Na_2SO_4. It was purified by column chromatography with 5 g of silica gel to yield 20 mg of an oily substance, yield 40%, $[\alpha]_D$-87° (c 0.16, $CHCl_3$). IR (KBr) cm^{-1} 3400 - 3500, 1725, 1655, 1505, 1490, 1460, 1370, 1270, 1230, 1075, 1035, 980. EIMS m/z 513 (M^+), 482, 329, 315, 314, 299, 298 (100), 284, 282, 266, 254, 228, 150. ^{1}HNMR ($CDCl_3$) δ ppm 6.55 (1H, s, C_{17}-H), 6.53 (1H, s, C_{14}-H), 6.28 (1H, s, C_3-H), 5.87 (1H, d, J = 9.6 Hz, C_3-H), 5.83 (2H, d, -OCH_2O-), 5.07 (1H, s, C_1-H), 3.81 (1H, d, J = 9.4 Hz, C_4-H), 3.71 (3H, s, -OCH_3), 3.70 (3H, s, -$COOCH_3$), 1.23 (3H, s, -CH_3), 1.17 (3H, s, -CH_3).

Compound 11

55 mg of *N*-ethanoyl-*N*-methyl-*L*-alanine was dissolved in 1 ml of dry tetrahydrofuran, and 0.1 ml of dry triethylamine and 0.025 ml of methyl sulphonyl chloride were added dropwise at -25°C with agitation under nitrogen protection. Agitation was continued for 1 h, and a solution of cephalotaxine (100 mg) and DMAP (8 mg) in dry tetrahydrofuran (0.5 ml) was then added slowly dropwise. It was agitated at room temperature overnight, and then diluted with dichloromethane. The organic layer was washed with 10% Na_2CO_3 and saturated saline and dried with anhydrous Na_2CO_3, and the solvent was evaporated off under reduced pressure. Purification was carried out by column chromatography with 10 g of silica gel, to yield 43 mg of colourless solid, yield 31%. $[\alpha]_D$-114.7° (c 0.28, $CHCl_3$). IR (KBr) cm^{-1} 1745, 1655, 1505, 1490, 1375, 1225, 1035, 930, 755. EIMS m/z 442 (M^+), 411, 315, 314, 299, 298 (100), 297, 282, 266, 150, 149, 128. ^{1}HNMR ($CDCl_3$) δ ppm 6.61 (1H, s, C_{17}-H), 6.56 (1H, s, C_{14}-H), 5.88 (2H, d, -OCH_2O-), 5.86 (1H, d, J = 9.1 Hz, C_3-H), 5.02 (1H, q, J = 7.2 Hz, C_2-H), 5.01 (1H, s, C_1-H), 3.76 (1H, t, J = 10 Hz, C_4-H), 3.68, 3.66 (3H, s, -OCH_3), 2.47, 2.78 (3H, s, N-CH_3), 1.96, 1.84 (3H, s, -$COCH_3$), 1.20, 1.09 (3H, d, J = 7.2 Hz, -CH_3).

Compound 12

55 mg of *N*-isobutanoyl-*N*-methyl-*L*-alanine was used according to the preparation method for 11, to yield 25 mg of solid, with a yield of 15%. $[\alpha]_D$-71° (c 0.39, $CHCl_3$). IR (KBr) cm^{-1}

1740, 1660, 1505, 1490, 1375, 1220, 1085, 1035, 930, 755. EIMS m/z 470 (M^+), 439, 315, 314, 299, 298 (100), 282, 266, 156, 150. ^{1}HNMR ($CDCl_3$) δ ppm 6.60 (1H, s, C_{17}-H), 6.56 (H, s, C_{14}-H), 5.88 (2H, m, -OCH_2O-), 5.88 (1H, m, C_3-H), 5.00 (1H, m, C_1-H), 4.93 (1H, q, J = 7.2 Hz, C_2-H), 3.77 (1H, m, C_4-H), 3.67 (3H, s, -OCH_3), 2.60, 2.45 (3H, s, NCH_3), 1.07 (3H, d, J = 6.8 Hz, -CH_3), 1.03 (6H, dd, J = 6.7 Hz, 2 × CH_3).

Compound 13

55 mg of *N*-ethanoyl-*L*-alanine was processed exactly as for the preparation of 11, to yield 67 mg of colourless solid, with a yield of 50%. $[\alpha]_D$-98° (c 0.67, $CHCl_3$). IR (KBr) cm^{-1} 3300, 1740, 1655, 1540, 1505, 1485, 1450, 1370, 1225, 1160, 1035, 920, 730. EIMS m/z 428 (M^+), 397, 315, 314, 299, 298 (100), 282, 266, 150. ^{1}HNMR ($CDCl_3$) δ ppm 6.60 (1H, s, C_{17}-H), 6.54 (1H, s, C_{14}-H), 5.84 (2H, s, -OCH_2O-), 5.82 (1H, d, J = 9.6 Hz, C_3-H), 5.53 (1H, m, NH), 5.04 (1H, s, C_1-H), 4.12 (1H, q, J = 7.2 Hz, C_2-H), 3.76 (1H, d, J = 9.5 Hz, C_4-H), 3.68 (3H, s, -OCH_3), 1.88 (3H, s, -$COCH_3$), 1.09 (3H, d, J = 7 Hz, -CH_3).

Compound 14

82 mg of *N*-*p*-toluenesulphonyl-*N*-methyl-*L*-alanine was used as for the preparation of 11, to yield 94 mg of colourless solid, with a yield of 53%. $[\alpha]_D$-81° (c 0.91, $CHCl_3$). IR (KBr) cm^{-1} 1750, 1690, 1660, 1505, 1490, 1375, 1340, 1220, 1170, 1080, 1040, 930, 750. EIMS m/z 554 (M^+), 523, 314, 299, 298 (100), 297, 282, 266, 212, 155, 150. ^{1}HNMR ($CDCl_3$) δ ppm 7.54 (2H, d, J = 8 Hz), 7.28 (2H, d, J = 8 Hz), 6.66 (1H, s, C_{17}-H), 6.56 (1H, s, C_{14}-H), 5.88 (2H, d, -OCH_2O-), 5.75 (1H, d, J = 9.4 Hz, C_3-H), 5.05 (1H, s, C_1-H), 4.24 (1H, q, J = 7 Hz, C_2-H), 3.75 (1H, m, C_4-H), 3.70 (3H, s, -OCH_3), 2.39 (6H, s, NCH_3, $PhCH_3$), 0.97 (3H, d, J = 7.2 Hz, -CH_3).

Compound 15

200 mg of phenyl-α-oxopropanoic acid was dissolved in 2 ml of dry benzene, and 307 mg of oxalyl chloride was slowly added dropwise at -5°C. It was agitated at room temperature for 3 h, and the solvent and oxalyl chloride were evaporated off under reduced pressure. 2 ml of

dry dichloromethane was added, to yield the working α-ketoyl chloride solution. A solution was made up by dissolving 300 mg of cephalotaxine in 0.4 ml of dry pyridine and 0.8 ml of dry dichloromethane. It was agitated at -5°C, and the abovementioned working solution was added slowly dropwise in the cold state, and agitation was continued for 3 h and left overnight at room temperature with agitation. The following day the temperature was raised to 40°C with further agitation for 2 h. An excess of diethylamine was added, and the solvent was evaporated off under reduced pressure. Dry benzene was then added, and the solvent again evaporated off under reduced pressure. Purification was carried out by column chromatography with 20 g of silica gel, to yield 170 mg of a pale yellow solid, yield 40%. $[\alpha]_D$-102° (c 2.2 $CHCl_3$). IR (KBr) cm^{-1} 1735, 1655, 1505, 1486, 1460, 1375, 1220, 1125, 1030, 930, 750. HRMS 442.2118, molecular formula $C_{24}H_{30}N_2O_6$. EIMS m/z 442 (M^+), 411, 314, 299, 298 (100), 282, 266, 150, 149. ^{1}HNMR (CD_3COCD_3) δ ppm 6.70 (1H, s, C_{17}-H), 6.66 (1H, s, C_{14}-H), 5.93 (2H, d, -OCH_2O-), 5.93 (1H, d, J = 9.6 Hz, C_3-H), 5.30 (1H, s, C_1-H), 3.98 (1H, d, J = 9.5 Hz, C_4-H), 3.72 (3H, s, -OCH_3), 1.00 (3H, t, J = 7.1 Hz, -CH_3), 0.91 (3H, t, J = 7.1 Hz, -CH_3).

Compound 16

30 mg of phenyl-α-oxopropanoic acid was dissolved in 1 ml of dry tetrahydrofuran, and 0.08 ml of dry triethylamine was added. 0.02 ml of methyl sulphonyl chloride was added dropwise at -30°C with agitation under nitrogen protection. Once the addition was complete, agitation was continued for 1 h, and then cephalotaxine (40 mg) and DMAP (5 mg) dissolved in dry tetrahydrofuran (0.5 ml) was added dropwise, and then the temperature was raised to 5°C and agitated for 6 h. Agitation continued overnight at 10°C. The following day the temperature was raised to 25°C and agitation was carried out for 6 h. The reaction liquid was poured into a 10% Na_2CO_3 aqueous solution, and extraction was carried out several times using dichloromethane and benzene. The organic layer was washed with a 50% saturated saline solution and dried with anhydrous Na_2SO_4. The solvent was evaporated off, and purification was carried out by column chromatography with 5 g of silica gel, to yield 50 mg of colourless solid, yield 73%, $[\alpha]_D$-118° (c 2.9, $CHCl_3$). IR (KBr) cm^{-1} 1720, 1645, 1485, 1365, 1260, 1220, 1180, 1080, 1030, 780, 690. HRMS 539.1609, molecular formula $C_{28}H_{29}NO_8S$. EIMS m/z 539 (M^+), 508, 461, 460, 315, 314, 299, 298 (100), 284, 282, 266,

225, 150. ^{1}HNMR (CD_3COCD_3) δ ppm 8.02 (1H, m, Ph-H), 7.73, 7.41 (4H, m, Ph-H), 6.83 (1H, s, CH=), 6.67 (1H, s, C_{17}-H), 6.62 (1H, s, C_{14}-H), 6.01 (1H, d, J = 9.4 Hz, C_3-H), 5.80 (2H, d, -OCH_2O-), 5.37 (1H, s, C_1-H), 4.00 (1H, d, J = 9.4 Hz, C_4-H), 3.75 (3H, s, -OCH_3), 3.37 (3H, s, -SO_2CH_3).

Compound 17

20 mg of sodium *p*-nitrophenyl methanoate was used in accordance with the preparation method for 12, to yield 25 mg of colourless solid, yield 68%. $[\alpha]_D$-253° (c 0.184, $CHCl_3$). IR (KBr) cm^{-1} 1730, 1655, 1528, 1505, 1486, 1345, 1275, 1225, 1110, 1035, 935, 860, 755, 720. EIMS m/z 464 (M^+), 449, 433, 330, 315, 314, 299, 298 (100), 284, 282, 267, 266, 254, 150, 149. ^{1}HNMR ($CDCl_3$) δ ppm 8.15, 7.80 (4H, m, Ph-H), 6.25 (1H, s, C_{17}-H), 6.46 (1H, s, C_{14}-H), 6.02 (1H, d, J = 10 Hz, C_3-H), 5.66 (2H, d, -OCH_2O-), 5.27 (1H, s, C_1-H), 3.94 (1H, d, J = 10 Hz, C_4-H), 3.67 (3H, s, -OCH_3).

Discussion

It can be seen from the screening results (Table 1) that compounds 11 - 14 and 17 had no activity. In all cases their side chains had no methyl ethanoate group, showing that a methyl ethanoate group in the side chain is an indispensable active group in the molecule. When the methyl ethanoate group was substituted by an unsaturated methyl ethanoate group and a methyl sulphonate group respectively, the activity was only of a moderate strength (10 and 16), further showing the invariability of the methyl ethanoate group.

The differences in the structures of compounds 1, 2 and 6 were only in the numbers of methylene groups in the R_1 group, and as the number of methylene groups (n) increased from 1 to 3, the activity of the compound against white mice leukaemia P 338 gradually fell. This shows that the R_1 group not only has the actions of adjusting lipophilicity and hydrophilicity of the molecule [5], but the size of the group also affects the activity of the molecule. When n = 1 and 2, the epimeric mixture of 1 and 2 + 3 had a significant suppressant action on P 388, and when the concentration was 1 μg/ml, its activity was equal to that of the control substance homoharringtonine. This result shows that with this kind of structure, the C_2 epimer has equivalent activity, indicating that it is unnecessary to separate the epimeric mixture. What is

interesting is the pharmacological results of the epimer pairs for the remaining two, namely that with a concentration of 1 μg/ml, 6 (2'*R*) was effective, while 7 (2'*S*) was ineffective; and the situation was exactly the opposite for the other pair, with 4 (2'*R*) showing no activity, and 5 (2'*S*) being active. The reasons for the above inconsistency may be that the R_1 group in 4 and 5 contained a double bond. This shows that it is not only the size of the R_1 group but also the spatial arrangement of the R_1 group which affects the anticancer activity of the molecule.

Harringtonine alkaloids derive their anticancer activity through suppressing protein synthesis, and their mechanism is different to that of ordinary anticancer active agents [9], and the exclusivity of their structure effect is very high. According to the pharmacological mechanism and the above results, we propose that, except for the R_1 and R_2 groups in the molecule, the remaining structure may not be changed. The $-OCH_2O-$, tertiary nitrogen, alkene methoxy group and double ester group form a definite cage structure, which plays a key role in the suppression of protein synthesis. When the size and spatial arrangement of this cage structure meet the requirements of the protein acceptor, chelation can take place with it, thus producing an anticancer action. The R_1 group, on the other hand, plays a role in adjusting the lipophilicity and hydrophilicity of the molecule. The R_1 group may be changed, but it is subject to certain limitations, and the magnitude of its change may not exceed the point where it affects the structure of the cage. If the volume of the R_1 group is too large, it will deform the cage structure, and the molecule will lose its activity.

[Formula]

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